LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

JAMES R. PHELPS
PAUL M. HYMAN
ROBERT A. DORMER
STEPHEN H. McNAMARA
ROGER C. THIES
THOMAS SCARLETT
JEFFREY N. GIBBS
BRIAN J. DONATO
FRANK J. SASINOWSKI
DIANE B. McCOLL
A. WES SIEGNER, JR.
ALAN M. KIRSCHENBAUM
DOUGLAS B. FAROUHAR
JOHN A. GILBERT, JR.
JOHN R. FLEDER
MARC H. SHAPIRO
ROBERT T. ANGAROLA
(1945-1996)

700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

MARY KATE WHALEN
OF COUNSEL

JENNIFER B. DAVIS
FRANCES K. WU
DAVID B. CLISSOLD
CASSANDRA A. SOLTIS
JOSEPHINE M. TORRENTE
MICHELLE L. BUTLER
PATRICIA A.A. VANSTORY
THOMAS R. GIBSON
LEIGH E. KENNEDY*
ANNE MARIE MURPHY
PAUL L. FERRARI
JEFFREY N. WASSERSTEIN
BRIAN J. MALKIN
MICHAEL D. BERNSTEIN
LARRY K. HOUCK*
DARA S. KATCHER*
KURT R. KARST*

*NOT ADMITTED IN DC

DIRECT DIAL (202) 737-4289

April 3, 2002

Dockets Management Branch
Food and Drug Administration
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

RE: Re: FDA Docket No. 01P-0396

FDA Docket No. 95N-0304

To Whom It May Concern:

Accompanying this letter is a joint response from five trade associations to the Public Citizen petition requesting a ban on ephedra dietary supplement products filed with the FDA in October 2001. The joint response is also being filed in the docket for the trade association's October 2000 petition to FDA requesting that the agency adopt the current industry and state standards for ephedra, as the joint response provides additional support for those standards.

The five trade associations that have signed the joint response are as follows: The American Herbal Products Association, the Consumer Healthcare Products Association, the Council for Responsible Nutrition, the National Nutritional Products Association, and the Utah Natural Products Alliance.

Sincerely,

A. Wes Siegner, Jr.

01P-0396

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2603 MAIN STREET
SUITE 760
IRVINE, CALIFORNIA 92614
(949) 553-7400
FAX: (949) 553-7433

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX: (919) 313-4751

April 2, 2002

The Honorable Tommy Thompson
Secretary of Health and Human Services
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Re: FDA Docket No. 01P-0396
FDA Docket No. 95N-0304

Dear Secretary Thompson:

Pursuant to 21 C.F.R. § 10.30(d), the undersigned Trade Associations (American Herbal Products Association, Consumer Healthcare Products Association, Council for Responsible Nutrition, National Nutritional Foods Association, and Utah Natural Products Alliance) submit these comments on the Citizen Petition filed by Public Citizen, in which that organization requested that the Food and Drug Administration (FDA) ban all dietary supplements containing ephedrine alkaloids and issue a warning advising all Americans not to use these products while FDA reviews Public Citizen's Petition. For the reasons set forth below, we request that FDA deny Public Citizen's Petition.

Put simply, Public Citizen's Petition must be denied for two reasons: (1) the Petition is based on adverse event reports, and FDA has already concluded that such reports do not represent a valid scientific basis for the regulation of ephedra; and (2) the Petition totally ignores the extensive data supporting the safety and benefits of ephedrine alkaloids and herbal ephedra, as well as the reviews of the relevant data that have been conducted by scientific and medical experts. The scientific data, as evaluated by recognized experts in a variety of fields, show that ephedra is safe when consumed according to strict standards that responsible manufacturers have adopted and that have been incorporated into several state laws, including Ohio, Washington, Hawaii, Michigan, Nebraska and Oklahoma. These standards, which include serving limits of 100 mg of ephedrine alkaloids per day and 25 mg per serving, are consistent with and supported by the comprehensive expert reviews of the supporting clinical data, including a risk assessment conducted by one of the most respected scientific consulting firms, Cantox Health Sciences International.

Consistent with the Citizen Petition that industry trade associations filed with FDA on October 25, 2000, Docket No. 95N-0304/CP2 (Trade Association Petition), and for other reasons stated below, the undersigned request that, in addition to denying Public Citizen's Petition, FDA adopt the standards set forth in the Trade Association Petition

either as regulations or as policy and that FDA withdraw the remaining portions of FDA's June 1997 proposed rule on ephedrine alkaloids.

I. PUBLIC CITIZEN HAS BASED ITS PETITION ON OLD INFORMATION THAT HAS BEEN REVIEWED, FOUND TO BE UNRELIABLE, AND REJECTED AS A BASIS FOR FDA ACTION

In its September 5, 2001 Citizen Petition, Public Citizen requested FDA to "ban the production and sale of dietary supplements containing ephedrine alkaloids" because "these products present 'a significant or unreasonable risk of illness or injury under conditions of use suggested or recommended in the labeling' or, if the label is not specific, 'under ordinary conditions of use.'" Public Citizen's Petition at 1. Public Citizen based its request almost entirely on adverse event reports (AERs) on ephedra that were reported to poison control centers and to the Center for Food Safety and Applied Nutrition's Special Nutritionals Adverse Event Monitoring System.

For example, Public Citizen noted that FDA's most recent analysis of the AERs "demonstrates that the ephedrine alkaloids are the most lethal and otherwise dangerous dietary supplements." Id. Public Citizen also relied on "a recent FDA analysis of [AERs] collected by the American Association of Poison Control Centers (AAPCC)" to support its position. Id. at 3. Examination of the references that Public Citizen cites in support of its Petition shows that the extensive clinical data supporting the safety of ephedrine alkaloids was ignored.

Public Citizen's Petition is therefore based on old information that has been considered, discussed and rejected as a basis for FDA action. Banning ephedra or even proposing regulations for ephedra based on AERs is not scientifically justifiable, due to the unreliability of these reports. FDA's withdrawal of much of its 1997 proposed rule to regulate dietary supplements containing ephedrine alkaloids best illustrates the problem with relying on AERs to support regulatory action. See Dietary Supplements Containing Ephedrine Alkaloids; Withdrawal in Part, 65 Fed. Reg. 17,474 (Apr. 3, 2000).

FDA withdrew portions of its proposed rule for various reasons, including the findings of a 1999 General Accounting Office (GAO) report that criticized FDA's reliance on AERs to determine dose and duration limits for these products. GAO, Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids 3 (July 1999). GAO stated that:

> Given the uncertainties in the information upon which FDA based its proposed rule, we recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to obtain additional information to support conclusions regarding the specific

> requirements in the proposed rule for dietary supplements containing ephedrine alkaloids before proceeding to final rulemaking. Specifically, FDA needs to provide stronger evidence on the relationship between the intake of dietary supplements containing ephedrine alkaloids and the occurrence of adverse reactions that support the proposed dosing levels and duration of use limits.

Id. at 24-25.

The "stronger evidence" that the GAO requested for a link between dietary supplements containing ephedrine alkaloids and the occurrence of adverse reactions does not exist in the clinical data – the clinical data instead support the safety and benefits of ephedra within the serving limits established by industry and state law. Therefore, FDA took the appropriate course and withdrew the portions of the proposed rule that the GAO had reviewed.

Public Citizen has based its petition on AERs that have been made public, thoroughly considered, and rejected as a basis for regulatory action. Therefore, basic, accepted scientific principle requires that FDA also reject Public Citizen's Petition[1].

II. PUBLIC CITIZEN HAS IGNORED ALL DATA SUPPORTING EPHEDRA SAFETY

Public Citizen's Petition focused on old issues, such as the AERs, without even mentioning the growing body of clinical data and other information that supports the safety and benefits of ephedra when these products are appropriately marketed and properly consumed. On October 25, 2000, FDA received a Citizen Petition submitted by the American Herbal Products Association, the Consumer Healthcare Products Association, the National Nutritional Foods Association, and the Utah Natural Products Alliance (Trade Association Petition). Unlike Public Citizen's Petition, the Trade Association Petition is based on the clinical literature that was available at that time, and

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[1] A recent public announcement by Canadian authorities to recall ephedra products that have been marketed in Canada, based on a much more limited sample of 60 AERs, does not add support to Public Citizen's Petition for two reasons. First, as the GAO and FDA recognize, regulatory action based solely on AERs for ephedra is not scientifically supportable. Second, the Canadian regulatory system is very different, and not subject to the same scientific scrutiny as the U.S. system. As is true of Public Citizen, Canadian authorities focused solely on AERs and ignored the considerable body of clinical data that is in direct conflict with their safety concerns.

is therefore based on valid science. The Trade Association Petition requested that FDA withdraw the remaining portions of its 1997 proposed rule and adopt instead the current voluntary industry standards for the formulation, labeling, and marketing of dietary supplements containing ephedrine alkaloids. These same standards have been adopted by a number of different states, including Ohio, Michigan, Washington, Nebraska, Oklahoma and Hawaii, effectively creating a national standard for ephedra products.[2] A copy of the Trade Association Petition is attached (Attachment A).

As a scientific basis, the Trade Association Petition cited comments of the Expert Panel of the Ephedra Education Council, submitted to FDA in October 2000. See Ephedra Education Council, Comments of the Expert Panel of the Ephedra Education Council on the Safety of Dietary Supplements Containing Ephedrine Alkaloids and on the AERs and the Health Assessments Released by the FDA on April 3, 2000 (Sept. 29, 2000) (Expert Panel's Comments). The Ephedra Education Council (EEC) Expert Panel's review involved experts from a variety of disciplines who reached consensus conclusions relevant to the safety of ephedra. The Expert Panel's Comments included an analysis of the published literature on the safety and usefulness of ephedra products and an analysis of published data on the incidence rates of seizures, strokes, and myocardial infarctions in the general population compared to estimates of incidence rates in consumers of ephedra products. The Expert Panel concluded that the "[a]vailable information does not demonstrate an association between the use of dietary supplements containing ephedrine alkaloids and serious adverse events when used according to the American Herbal Products Association (AHPA) trade recommendation for ephedra products." Expert Panel's Comments at 6.

FDA has yet to respond to the Trade Association Petition, other than to say that "we have not been able to reach a decision on your petition within 180 days of the filing of the petition because of the complexity and public health significance of the issues." Letter from Ms. Christine Lewis, FDA, to Hyman, Phelps & McNamara, P.C. (Apr. 20, 2001).

Since the Trade Association Petition was filed, two new reviews of ephedra products have been concluded, and the results of several new clinical studies have been published. All of these provide important confirmation of the safety of ephedra when consumed according to the standards set forth in the Trade Association Petition and established by state laws. Further, the new clinical studies confirm that ephedra products are one of the most important tools available to consumers who need to lose weight. Considering the enormous public health problems that Americans face as the direct result

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[2] Haw. Rev. Stat. § 329-64(a)(5); Mich. Comp. Laws § 333.7220(c)(ii); Neb. Rev. Stat. § 28-405(Schedule IV)(g)(3); Ohio Rev. Code Ann. § 3719.44(K)(2); Okla. Admin. Code § 475:10-1-24; Wash. Admin. Code § 246-883-030.

of unwanted and excess weight, the clinical data show that banning ephedra as requested by Public Citizen would be a serious public health mistake.

The new information that supports the Trade Association Petition, most of which was available to Public Citizen but was nowhere mentioned in its Petition, includes the following:

(1) Attachment B: A safety assessment of ephedra by Cantox Health Sciences International, a scientific consulting company specializing in safety and regulatory issues of products and processes as they affect human health and the environment. See Cantox Health Sciences International, Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra (Dec. 19, 2000). The Cantox Report has been provided to FDA, and is available from the Council for Responsible Nutrition through their website at http://www.CRNUSA.org. Cantox conducted a comprehensive review of information that related in any way to the safety of ephedra, including 19 clinical trials and numerous animal studies. The safe upper limit of 90 mg of ephedrine alkaloids, and the lowest observed adverse effect level of 150 mg, were determined using the National Academy of Sciences Upper Limit Model for nutrients. The Cantox report is the only safety assessment of ephedra using widely accepted procedures for conducting risk assessments. The Cantox serving limits are derived in part from the safety data generated in a clinical trial that utilized ephedrine alkaloid intakes of 30 mg per dose and 90 mg per day. The mild, non-adverse effects observed at the 30/90 level of intake, and the occurrence of only moderate adverse effects at the lowest observed adverse effect level of 150 mg, indicate that intakes of 25 mg per serving and 100 mg per day are likely to be safe. This conclusion is strongly reinforced by the lack of any established adverse effects of products used according to label instructions within this 25/100 standard. This lack of attributable adverse effects has persisted in the face of increasing sales of ephedra dietary supplement products over the last several years and has coincided with the acceptance of the 25/100 limits as a widely used industry standard and as the legal standard in several states. The Cantox risk assessment is consistent with and strongly supports the 25/100 standard, even though the Cantox assessment resulted in a slightly higher single-serving limit and a slightly lower daily limit.

(2) Attachment C: A published abstract reporting the findings from a randomized, double-blind, placebo-controlled six-month safety and efficacy trial on herbal ephedra and caffeine for weight loss. See C. N. Boozer et al., Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Safety and Efficacy Trial, 9 Obesity Research 68 (2001). The study's researchers, who are from Columbia and Harvard Universities, concluded that the combination herbal ephedra/caffeine product lowered body weight, fat, and body mass index with only minor, expected and transient adverse effects.

(3) Attachment D: A randomized, double-blind eight-week trial conducted on the effects of an ephedra/caffeine combination dietary supplement on weight loss. See C.

N. Boozer et al., An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: A Randomized, Double-Blind Trial, 25 International Journal of Obesity 316 (Mar. 2000). The study's researchers concluded that the herbal mixture "effectively promoted short-term weight and fat loss." Id. at 316. They also concluded that "[n]o subject had any serious or lasting adverse event in this relatively short-term and small-scale study," that additional studies were warranted, and that one long-term study, identified above, was already underway. Id. at 323.

(4) Attachment E: A review of the literature in Medline pertaining to the use of caffeine and ephedrine in the treatment of obesity. See F. Greenway, M.D., The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent, 2 Obesity Reviews 199 (2001). The author of the review concluded that caffeine and ephedrine are effective in causing weight loss, and this benefit outweighs the small risks associated with the consumption of these substances.

(5) Attachment F: A double-blind placebo controlled clinical study published in abstract form. See L. de Jonge et al., Safety and Efficacy of an Herbal Dietary Supplement Containing Caffeine and Ephedra for Obesity Treatment, 9 Obesity Research 184s (Supp. 3, Sept. 2001). The authors of this study, conducted at the Pennington Biomedical Research Center, concluded that caffeine and ephedra "increased metabolic rate and gave weight loss safely in this 3-month trial." Id.

(6) Attachment G: A published abstract reporting the findings of a blinded, controlled study, conducted at the University of Guelph on a commercial ephedra/caffeine product. See L. Belfie et al., Safety and Effectiveness of an Herbal Dietary Supplement Containing Ephedra (Ma Huang) and Caffeine (Guarana Extract) When Used in Combination with a Supervised Diet and Exercise Intervention, 9 Obesity Research 186s (Supp. 3, Sept. 2001). "This study shows that the caffeine/ephedra [product] had only mild side effects when taken in a controlled manner . . . ." Id.

Public Citizen's Petition should be rejected for failure to meet the requirements of FDA's regulations, which require petitioners to certify that they have provided "all information and views on which the petition relies, [including] representative data and information known to the petitioners which are unfavorable to the petition." 21 C.F.R. § 10.30(b). Public Citizen and Dr. Ray Woosley, who also signed Public Citizen's Petition, were certainly aware of much, if not all, of the information above. A simple review of the FDA docket would have made any petitioner aware of the EEC Panel Report and the Cantox Report, as well as other "representative data and information . . . unfavorable to the petition." A search of readily available computer databases would have produced cites to the Greenway article and other published data supporting the safety and benefits of ephedra. Yet Public Citizen's Petition excludes any mention of unfavorable information, but includes the "Certification" required by 21 C.F.R. § 10.30(b). Public Citizen's Petition states that "We certify that, to our best knowledge and belief, this petition includes all information and views which [sic] the petition relies,

and that it includes data and information known to the petitioners which are unfavorable to the petition."

Public Citizen and Dr. Woosley ignored an important part of the certification requirement, which is to provide all data and information unfavorable to the petition. The petition therefore violates FDA's regulations and must be rejected.

Even if Public Citizen's Petition had met the certification requirement, it should be rejected because it ignores the extensive scientific data that support ephedra safety and demonstrate the tangible health benefits of ephedra products for those who need to lose weight. The reviews and published clinical studies mentioned above, as well as other published studies that are not cited but are included in the Cantox Report and the EEC Expert Panel Report, all contradict the safety concerns that Public Citizen has raised in its petition. The petition must be denied for this reason as well.

III. CONCLUSION

Public Citizen's request that FDA ban dietary supplements containing ephedrine alkaloids should be denied because it is based on AERs, which do not serve as a scientific basis for regulatory action. There are, however, scientific data to support the regulatory action requested in the Trade Association Petition, and the undersigned Trade Associations request that FDA review the clinical data provided in that petition as well as the new clinical data provided with this response to the Public Citizen Petition, and that FDA adopt the standards set forth in the Trade Association Petition[3].

American Herbal Products Association

Consumer Healthcare Products Association

Council for Responsible Nutrition

National Nutritional Foods Association

Utah Natural Products Alliance

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[3] A copy of these comments on Public Citizen's Petition and the new clinical data attached to these comments will be added separately to the docket of the Trade Association Petition, Docket No. 95N-0304.